Circulating tumor DNA assay and survival in patients with metastatic, non-small cell lung cancer

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INTRODUCTION AND PURPOSE

- Circulating tumor DNA (ctDNA) sampling has emerged as a non-invasive approach that may be used to guide cancer treatment and prognosis.
- ctDNA can characterize genomic alterations in blood of patients (pts) with metastatic, non-small cell lung cancer (mNSCLC).
- We evaluated the relationship between ctDNA features and progression-free survival (PFS) in mNSCLC pts.

METHODS

- A prospective pilot study of 27 pts with histologically confirmed mNSCLC was conducted.
- Tumor specimens were collected within 30 days prior to baseline (prior to initiation of a new line of therapy).
- Blood specimens were collected at baseline, prior to cycles 2 and 3, and then every 6-8 weeks until progression.
- Radiology scans were performed at standard intervals.
- ctDNA was assessed by Inivata (InvisionFirst® - Lung) using amplicon-based targeted next generation sequencing with 36-gene panel to detect single nucleotide variants, short insertions/deletions, copy number variations and structural variants.
- ctDNA features were calculated for each pt and included number of genomic alterations (numGA), number of mutations (numMUT), number of amplifications/fusions (numAMPFUS), sum mutant allele frequency (sumMAF), and maximum mutant allele frequency (maxMAF).
- ctDNA from baseline (T0) to the blood collection closest to progression or censor date (T1) was used to assess change in sumMAF and maxMAF.
- Univariate and multivariable Cox proportional hazards models were used to identify ctDNA features associated with progression-free survival (PFS). All models included ctDNA features as continuous variables.
- Stratified PFS analyses were conducted to compare at least 1 Amp Fus vs 0 Amp Fus or high vs low sumMAF/maxMAF (stratified at the median).

Table 1. Patient Demographics

	N	%
Age		
Under 50	5	18.5
50-59	3	11.1
60-69	9	33.3
70+	10	37.0
Sex		
Male	10	37.0
Female	17	63.0
Race		
White	23	85.2
Black	1	3.7
Other	3	11.1
Hispanic		
No	25	92.6
Yes	1	3.7
Unknown	1	3.7

Table 2. Disease Characteristics

	N	%
Disease Type		
Adenocarcinoma	23	85.2
Squamous	4	14.8
History of Systemic Therapy		
Yes	11	40.7
No	16	59.3
History of Radiation		
Yes	12	44.4
No	15	55.5
Line of Treatment on Study		
1	18	66.7
2	2	7.4
3	3	11.1
4	2	7.4
5	2	7.4

Figure 1. Distribution of Genomic Alterations in Patients

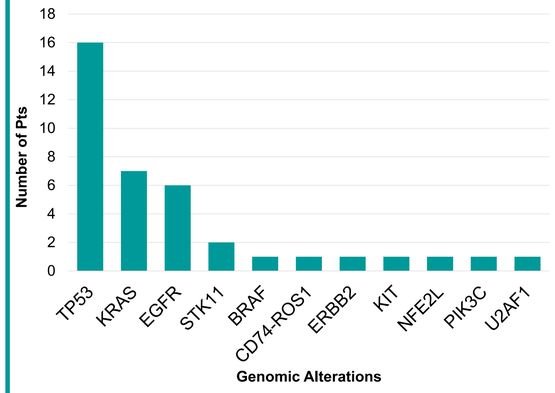
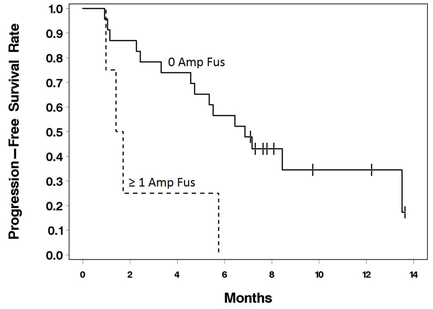


Table 3. Median Number of ctDNA Features

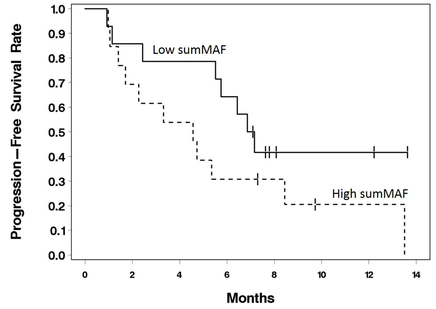
ctDNA Feature	Median (N)
numGA	2.00
numMut	2.00
numAMPFUS	0.00
maxMAF	1.61
sumMAF	2.34

Figure 2 and Table 4. Stratified PFS Analysis Results for at Least 1 Amp Fus vs 0 Amp Fus



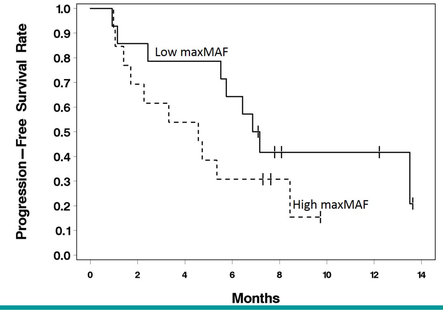
	≥ 1 Amp Fus	0 Amp Fus
N	4	23
PFS events	4	15
Median PFS (mos)	1.56	6.87
HR (95% CI) ref: 0 Amp Fus	4.325 (1.322, 14.151)	
P-value	0.009	

Figure 3 and Table 5. Stratified PFS Analysis Results for High sumMAF vs Low sumMAF



	High sumMAF	Low sumMAF
N	13	14
PFS events	11	8
Median PFS (mos)	4.57	7.01
HR (95% CI) ref: Low sumMAF	1.995 (0.791, 5.029)	
P-value	0.136	

Figure 4 and Table 6. Stratified PFS Analysis Results for High maxMAF vs Low maxMAF



	High maxMAF	Low maxMAF
N	13	14
PFS events	10	9
Median PFS (mos)	4.57	7.01
HR (95% CI) ref: Low maxMAF	1.924 (0.752, 4.928)	
P-value	0.165	

RESULTS

- Patient demographics and disease characteristics are presented in tables 1 and 2.
- 81.48% of pts had at least one genomic alteration detected in ctDNA at baseline.
- TP53, KRAS, and EGFR were the most frequently identified genomic alterations, presented in figure 1.
- EGFR alterations were the most commonly identified genomic alteration in ctDNA. 86.00% of EGFR alterations were actionable.
- Table 3 presents the median number of ctDNA features identified in blood specimens.
- Univariate Cox regression analysis identified numAMPFUS (HR=3.12, p=0.01), sumMAF (HR=1.02, p=0.02), and maxMAF (HR=1.05, p<0.01) to be significantly associated with PFS.
- Only maxMAF was retained in the final multivariable Cox model. Each percentage point increase in maxMAF from T0 to T1 resulted in a 4% decrease in the risk of progression/death (HR=0.96, p=0.08).
- Stratified analyses showed: worse PFS for subjects with at least 1 Amp Fus; numerically only worse PFS for subjects with high sumMAF/maxMAF.
- Although PFS correlated with quantitative changes in maxMAF from T0 to T1, stratified analyses did not suggest marked differences between low and high groups.

CONCLUSIONS

- In this pilot study, pts with higher levels of baseline maxMAF detected in ctDNA were associated with increased risk of progression/death.
- Due to small sample size considerations, observed differences are only hypothesis generating and negative results are not conclusive.
- ctDNA profiling may contribute to the prediction of PFS in mNSCLC pts.
- Future research using a larger sample size is warranted.

INFORMATION

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